IN THE CLAIMS

Please cancel Claims 1-6 and 18-21, without prejudice or disclaimer, since these claims are drawn to a non-elected invention.

REMARKS

Reconsideration is respectfully requested for Claims 7 and 9-17, said claims having been rejected under 35 U.S.C. 112, the Examiner alleging, in substance, that there is insufficient disclosure in the specification for the term *upregulating agent*. This rejection is respectfully traversed.

It is respectfully submitted that the expressions *upregulated agent*, *to upregulate*, and their derivative forms such as *upregulate*, *upregulation*, *upregulated*, and *upregulating*, are clearly understood by those skilled in this art.

Although there is no specific verb form "to upregulate", nor its derivative forms upregulate, upregulation, upregulated, and upregulating are found in the standard American Heritage Dictionary of the English Language, these terms have their root in the well understood verb form, to regulate. Moreover, the concept of upregulation is well understood by scientific practitioners as meaning an increase in the expression or amount of a particular substance. In support of this contention, a search was performed in the National Center for Biotechnology Information's PubMed database for the inclusive years 1980 to 2003 and found that the term upregulating was used in 715 biomedical research papers; the term upregulate was used in 2153 biomedical research papers, the term upregulates in 1799 papers, the term upregulated in 9872 papers and the term upregulation was used in 24,123 research papers. The first listed paper in

the upregulation database series, Rohatgi et al., J. Neurosci. Res., 1980,73:246-254 used the terms upregulated and upregulation in the following sentence: "Levels of PAR mRNA for all four subtypes were upregulated as early as 6hr after unilateral ONC, except PAR-3, which showed a delayed upregulation." In this article, the substances that increase in expression or amount are the mRNAs for protease-activated receptors (PARs). The final paper listed in this enormous database is an article by Takeuchi et al., Am. J. Physiol., 2003, 238:G135-140, that used the term upregulation in the following manner: "The upregulation of the gastrin receptor was evident if the binding capacity was expressed per milligram of protein, per microgram of DNA, or per amount of 125I-labeled choleragen bound to the same membrane preparation". In this paper, the substance that was increased in expression or amount was the receptor for the hormone gastrin. Although these papers were published 22 years apart, they used the term upregulation in the same way.

The first paper in the upregulating database series, Masri, Mol. Immunol. 1980, 39:1073-1077, used the term upregulating in the following sentence: "Recently, antibodies to the CD40/CD40 ligand have been shown to induce long-term graft survival with the inhibition of the Th1 cytokines (INF), IL-2 and IL-12 and upregulating the Th2 cytokines IL-4 and IL-10". Here, the term upregulating refers to increased expression of the TH2 cytokines IL-4 and IL-10. The final paper in this series, Fiorilli et al., Surv. Immunol. Res., 4 Suppl. 1:129-134, 1985, uses upregulating in the following manner: "The possibility of upregulating the immunoglobulins is of particular relevance in patients with hypogammaglobulinemias and this paper reports on the results of thymopentin treatment in 9 patients with selective IgA deficiency". In this case, the substance that is increased in expression is immunoglobulin. Interestingly, one skilled in the art would immediately recognize thymopentin as the "upregulating agent" for immunoglobulin.

As used in the instant specification and claims, the specific function of the upregulating agent is to increase the expression or amount of B7 family costimulatory genes and molecules in antigen presenting cells. For instance, in the specification, on p. 6 beginning at sentence 16 it is stated, "At the same time, in order for the macrophage to be an effective APC, it must upregulate the expression of B7 genes, and begin to express large amounts of B7 costimulatory molecules on its surface". Then in the next sentence, "It is presently unclear just what microbial products are responsible for causing the upregulation of the B7 gene, and indeed, not all microorganisms ingested by macrophages cause the increased expression of B7 molecules (Gupta et al., Eur. J. Immunol., 1996, 26:563-70)". It is thus respectfully submitted that an artisan would have a clear understanding of the terms upregulate and upregulation, and would know that this references the increased expression of the B7 gene and the B7 molecule. Furthermore, on p. 7, sentence 8, "We sought to identify a safe and effective pharmacologic agent that could upregulate the expression of the critical B7 costimulatory molecule on APC". One skilled in the art would clearly understand the use of the term upregulate, and by simple extension, would recognize the pharmacologic agent as an "upregulating agent". A still further example of the clear and concise use of the derivative term is found beginning on p. 7, sentence 21, "The b-1,3-glucans have been administered to animals and humans for years with no untoward effects, so we wondered whether this class of pharmacologic agents would upregulate the cell surface expression of B7 molecules on macrophages". A layman might choose to use the terms "increase" or "increasing" in place of "upregulate" or "upregulating" to confer the idea that there is more of a substance present as the result of the use of the agent. However, to an artisan skilled in the art of molecular biology, the terms upregulate and upregulating have clear meaning.

In Claim 7, the term *upregulating agent* is clearly associated with the <u>function</u> of

increasing the number of B7 molecules on the surface of an antigen-presenting cell. Indeed, the last phrase of Claim 7 reads, "allowing an **upregulation** (emphasis added) of B7 molecules on a cell whereby an expression of the B7 molecules allows reaction with an effector cell, the reaction with the armed effector cell potentiating an immune response". In concert with the adequate description of the function of upregulating B7 gene and protein expression given in the specification (described above), and the documented use of the term upregulation and its derivatives by scientific practitioners, it is respectfully submitted that the instant specification, as well as Claims 7 and 9-17, fully comply with 35 U.S.C. 112.

Reconsideration is also respectfully requested for Claims 7, 8, 13, 22 and 23 under 35 U.S.C. 102 based upon U.S. Patent No. 5,401,727 to Rorstad et al (the '727 patent). This rejection is respectfully traversed.

It is well known in the art that β-glucans enhance immune responses and provide resistance to disease in animals and humans (see review by DiLuzio, Trends Pharmacol. Sci. 1983, 4:344-347, as referenced in the instant specification). Claims 7, 8, 13, 22 and 23 are distinguished from this body of prior art in that they call for the novel use of β-glucans to potentiate immune responses that require enhanced expression of B7 costimulatory molecules on antigen presenting cells. U.S. Patent No. 5,401,727 to Rorstad et al. covers the use of β-glucans for enhancing the immune response of fish in the class Osteichthyes and invertebrates in the subphylum Crustacea. Nowhere in the '727 patent disclosure does it suggest that β-glucan serves as an upregulating agent for the expression of B7 molecules on antigen-presenting cells. Indeed, to the best of our knowledge, it has not been demonstrated that either fish in the class Osteichthyes or invertebrates in the subphylum Crustacea possess B7 family molecules on the surface of their antigen-presenting cells. Therefore, it would not be obvious to one skilled in the art, having read the teachings of the Rorstad et al. patent, that β-glucans would function to

upregulate the expression of B7 family costimulatory molecules on antigen presenting cells. It is therefore respectfully submitted that Claims 7, 8, 13, 22 or 23 are not anticipated by the '727 patent.

Reconsideration is respectfully requested for Claims 7-17 and 22-24, said claims having been rejected under 35 U.S.C. 103 as being unpatentable over the '727 patent to Rorstad, et al in view of the '776 patent to Ostrand-Rosenberg, et al. This rejection is respectfully traversed.

U.S. Patent No. 5,858,776 to Ostrand-Rosenberg, et al (the '776 patent), cited by the Examiner when viewed with the '727 patent to Rorstad et al, likewise provides no teaching which would cause Claims 7-17 and 22-24 to be obvious under 35 U.S.C. 103. There is no suggestion in the '776 patent to lead one skilled in this art to know, or even suspect, that β-glucans would upregulate the expression of B7 family molecules on the surface of antigen presenting cells. The Ostrand-Rosenberg et al. patent is directed to causing tumor cells to express costimulatory molecules such as B7 family costimulatory molecules, for the purpose of the T-lymphocyte-mediated immune response to the tumor cells. The '727 patent seems to suggest that in the small subset of tumors that have the capacity to express costimulatory molecules, but either do not express these molecules or express them in levels too low to interact productively with T-cells, "agents" could be used to cause these tumor cells to increase the expression of the costimulatory molecules. Though no examples are given, Ostrand-Rosenberg et al. mention the use of three potential B7 upregulating agents: dibutryl cAMP, anti-MHC antibodies, and a nucleic acid encoding a transcription factor which "upregulates transcription of the gen encoding the costimulatory molecule". None of these upregulating agents is related to the β-glucans physically or chemically, and knowledge of the function of these agents in upregulating costimulatory molecules would not have lead an artisan to even suspect that β-glucans would perform this function. Indeed, β-glucans are not mentioned in the Ostrand-

Rosenberg et al. patent. Moreover, the other teachings of the Ostrand-Rosenberg et al. patent mentioned by the Examiner (e.g., those describing the function of B7 costimulatory molecules) are well known from other sources. For instance, in the instant specification, beginning on sentence 2, there is described the costimulatory second signal delivered by B7 family molecules upon interaction with T-lymphocytes, and there are cited a variety of references including Razi-Wolf, et al., Proc. Natl. Acad. Sci. USA, 1992, 89:4210-14, published one year before the listed filing data of the Ostrand-Rosenberg et al. patent application (Nov. 3, 1993). Knowledge of these references published in the open scientific literature, and more particularly, knowledge of the teachings of the Ostrand-Rosenberg et al. patents, would not lead an artisan to know or even to suspect that β-glucans would upregulate the expression of B7 family costimulatory molecules on antigen presenting cells.

Finally and importantly, the combined teachings of Rorstad et al. (the '727 patent) and Ostrand-Rosenberg et al. (the '776 patent) would not lead one skilled in the art to know or even to suspect that β-glucans would function to upregulate the expression of the B7 family costimulatory molecules on antigen presenting cells. Although Rorstad et al. teaches that β-glucans enhance resistance to disease in fish and crustacea, knowledge of this and the teachings of Ostrand-Rosenberg et al. would not lead an artisan to know or anticipate that β-glucans would upregulate the expression of B7 molecules on antigen presenting cells in animals or humans (nor in fish or crustacea for that matter). Although Ostrand-Rosenberg et al. teaches that enhanced expression of B7 costimulatory molecules on tumor cells can improve the T-lymphocyte-mediated immune response to these tumors, and further suggests that "agents" could be used to accomplish this upregulation, knowledge of this and the teachings of Rorstad et al. would not lead an artisan to know or anticipate that β-glucans would upregulate the expression of B7 molecules on antigen presenting cells.

In summary, since neither the '727 patent nor the '776 patent, each taken alone, disclose or even suggest that β-glucans would function to upregulate the expression of B7 family costimulatory molecules on antigen presenting cells, there certainly is no such teaching or suggestion if the two references are combined to provide a basis for rejection under 35 U.S.C. 103.

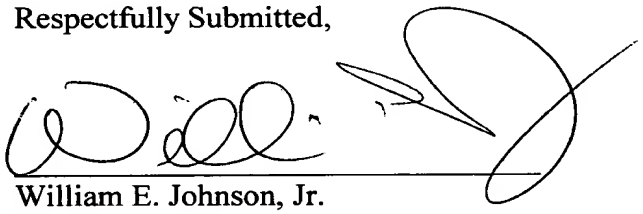
Accordingly, Claims 7-17 and 22-24 are respectfully submitted to be fully compliant with 35 U.S.C. 112, and to be patentable over the cited art of record, for the reasons as set forth above.

The undersigned attorney for the applicants would welcome a telephone conference with the Examiner, provided, of course, the Examiner believes this would be helpful in advancing this application to issue.

CHANGE OF RESPONSIBILITY

Please not that the undersigned attorney for the applicants' is now the Attorney in Charge of this application. Accordingly, all further correspondence, telephone calls and the like should be directed to the undersigned attorney.

Respectfully Submitted,



William E. Johnson, Jr.
Reg. No. 22,719
THE MATTHEWS FIRM (Cust. No. 021897)
1900 West Loop South, Suite 1800
Houston, Texas 77027
713-355-4200 - Telephone
713-355-9689 - Facsimile